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9929547.9 14 December 1999 (14.12.1999) GB

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(72) Inventors; and

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Published:

— with international search report

(88) Date of publication of the international search report:  
15 November 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/02594 A3

(54) Title: DNA CONSTRUCTS BASED ON THE eIF4A GENE PROMOTER

(57) Abstract: The present invention provides novel DNA constructs comprising a transcriptional regulatory sequence comprising a polynucleotide derivable from the eIF4A1 gene promoter. In preferred embodiments, the polynucleotide further comprises a polynucleotide derivable from the eIF4A gene introns, particularly intron 1. Host cells harbouring the constructs are also provided. These novel constructs have applications in gene therapy, DNA vaccines and in the commercial production of proteins.

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**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7	C12N15/85	C12N15/12	C12N5/10	A61K31/17
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According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBL

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KUKIMOTO I. ET AL.: "Characterization of the cloned promoter of the human initiation factor 4AI gene" BIOCHEM. BIOPHYS. RES. COM., vol. 233, 1997, pages 844-847, XP002152479 cited in the application the whole document	1,6,7, 9-17,20
A	---	2-5,18, 19 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "U" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

29 January 2001

02 02 2001

Name and mailing address of the ISA

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# INTERNATIONAL SEARCH REPORT

International Application No  
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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>QUINN C.M. ET AL.: "The human eukaryotic initiation factor 4AI gene (EIF4AI) contains multiple regulatory elements that direct high-level reporter gene expression in mammalian cell lines"  <b>GENOMICS</b>, vol. 62, 15 December 1999 (1999-12-15), pages 468-476, XP002152480 the whole document          -&amp; DATABASE EMBL SEQUENCES [Online]          Accession No. AF175325, 15 February 2000 (2000-02-15)          QUINN C.M.: "H. sapiens EIF4AI gene"          XP002152482</p> <p>---</p>	1-20
X	<p>WO 97 42337 A (GLAXO GROUP LTD ;GREAVES DAVID ROBERT (GB)) 13 November 1997 (1997-11-13) seq. 3: compare nt 1-357, 468-646, 791-871 and 1220-1467 with seq. IDs 34 (nt 7-363), 35, 36, 37, respectively.</p> <p>---</p>	18
X	<p>DATABASE EMBL SEQ. [Online]          Accession No. HS944183, 6 August 1995 (1995-08-06)          "EST; H. sapiens cDNA clone IMAGE:187152"          XP002152483          compare with nt 632-926 of seq. 31</p> <p>---</p>	18
X	<p>DATABASE EMBL SEQUENCES [Online]          Accession No. HS011206, 7 October 1995 (1995-10-07)          "EST; H. sapiens cDNA clone IMAGE:204614 similar to eukaryotic initiation factor 4A-I."          XP002152484          compare nt 1-180 with nt 58-237 of seq. 32</p> <p>---</p>	18
X	<p>DATABASE EMBL SEQUENCES [Online]          Accession No. HSU79273, 14 December 1996 (1996-12-14)          ANDERSSON B.: "Human clone 23933 mRNA"          XP002152485          compare nt 3-373 with nt 18-390 of seq. 33</p> <p>---</p> <p style="text-align: center;">-/-</p>	18

# INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL SEQUENCES [Online]            Accession No. AB011595,            10 March 1998 (1998-03-10)            "Mouse eIF4A gene"            XP002152486            compare nt 740-1462, 3722-3999 and            4358-4425 with seq. IDs 31 (nt 240-963),            34 (nt 38-359) and 36 (nt 1-69),            respectively.            -&amp; MIYASHITA A. ET AL.: "Five different            genes, Eif4a1, Cd68, Sup115h, Sox15 and            Fxr2h, are clustered in a 40 kb region of            mouse chromosome 11"            GENE,            vol. 237, no. 1,            3 September 1999 (1999-09-03), pages            53-60, XP004183497</p> <p style="text-align: center;">---</p>	18
A	<p>JONES E. ET AL.: "The linked human            elongation initiation factor 4A1 (eIF4A1)            and CD68 genes map to chromosome 17p13"            GENOMICS,            vol. 53, 15 October 1998 (1998-10-15),            pages 248-250, XP002157483            the whole document</p> <p style="text-align: center;">-----</p>	1-20

## PCT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PG3717</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 00/ 02569</b>	International filing date (day/month/year) <b>05/07/2000</b>	(Earliest) Priority Date (day/month/year) <b>06/07/1999</b>
Applicant <b>GLAXO GROUP LIMITED et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

DNA CONSTRUCTS BASED ON THE EIF4A GENE PROMOTER

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

None of the figures.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 00/02569

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  

Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/MSA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 2-5,8,18 and partly 1,6,7,9-17

A DNA construct comprising a transcriptional regulatory sequence operatively linked to a heterologous gene of interest, wherein the transcriptional regulatory sequence comprises the eIF4A gene promoter, a fragment thereof or a polynucleotide hybridisable thereto, and further comprises at least one eIF4A intron, fragment thereof or polynucleotide hybridisable thereto.

Recombinant host cells, methods of production, pharmaceutical compositions, therapeutic applications.

An isolated polynucleotide having a sequence as set forth in seq. IDs 31-37, a fragment thereof or a polynucleotide hybridisable thereto.

2. Claims: 19,20 and partly 1,6,7,9-17

A DNA construct comprising a transcriptional regulatory sequence operatively linked to a heterologous gene of interest, wherein the transcriptional regulatory sequence is an eIF4A gene promoter fragment selected from -526EIF, -371EIF, -271EIF, -193EIF, -120EIF, -98EIF, -69EIF, -40EIF, and seq. ID 38. Recombinant host cells, methods of production, pharmaceutical compositions, therapeutic applications.

An isolated polynucleotide having a sequence as set forth in seq. ID 40 at position -2102 and -1082 or at positions -1107 to -505, or respective fragments thereof or polynucleotides hybridisable thereto.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/02569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9742337 A	13-11-1997	AU 2705497 A EP 0914456 A	26-11-1997 12-05-1999

## PATENT COOPERATION TREATY

PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT



(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PG3717	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB00/02569	International filing date (day/month/year) 05/07/2000	Priority date (day/month/year) 06/07/1999
International Patent Classification (IPC) or national classification and IPC C12N15/85		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I    Basis of the report
- II    Priority
- III    Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV    Lack of unity of invention
- V    Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI    Certain documents cited
- VII    Certain defects in the international application
- VIII    Certain observations on the international application

Date of submission of the demand 23/01/2001	Date of completion of this report 16.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Rojo Romeo, E  Telephone No. +49 89 2399 7321



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/02569

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-34                   as originally filed

**Claims, No.:**

1-19                   as received on                   02/10/2001   with letter of                   02/10/2001

**Drawings, sheets:**

1/10-10/10           as originally filed

**Sequence listing part of the description, pages:**

1-23, filed with the letter of 27.09.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY  
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International application No. PCT/GB00/02569

the description,      pages:  
 the claims,           Nos.:  
 the drawings,        sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):  
*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**II. Priority**

1.  This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:  
 copy of the earlier application whose priority has been claimed.  
 translation of the earlier application whose priority has been claimed.

2.  This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:  
**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:  
 the entire international application.  
 claims Nos. 18, 19 (entirely); 1, 6, 8-16 (partially).

because:

the said international application, or the said claims Nos. 18, 19 (entirely); 1, 6, 8-16 (partially) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/02569

- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:
  - restricted the claims.
  - paid additional fees.
  - paid additional fees under protest.
  - neither restricted nor paid additional fees.
2.  This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
  - complied with.
  - not complied with for the following reasons:
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
  - all parts.
  - the parts relating to claims Nos. 2-5, 7, 17 (entirely); 1, 6, 8-16 (partially).

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims 1-16
	No: Claims 17
Inventive step (IS)	Yes: Claims 2-7, 10-16

**INTERNATIONAL PRELIMINARY  
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International application No. PCT/GB00/02569

No: Claims 1, 8 (partially), 9 (partially), 17

Industrial applicability (IA) Yes: Claims 12, 15 (see separate sheet)

No: Claims

2. Citations and explanations  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02569

**Re Item I**

**Basis of this report**

Concerning the following comments, the Applicant's letter of 02.10.01 was carefully considered.

The present set of claims seems to comply with Art. 19(2) PCT.

**Re Item II**

**Priority**

As far as invention 1 is concerned, it seems that the right of priority can be acknowledged. Consequently, the following documents may not be relevant for the assessment of novelty:

D7: QUINN C.M. ET AL.: 'The human eukaryotic initiation factor 4AI gene (EIF4AI) contains multiple regulatory elements that direct high-level reporter gene expression in mammalian cell lines' GENOMICS, vol. 62, 15 December 1999 (1999-12-15), pages 468-476, XP002152480 -& DATABASE EMBL SEQUENCES [Online] Accession No. AF175325, 15 February 2000 (2000-02-15) QUINN C.M.: 'H. sapiens EIF4A1 gene' XP002152482

D8: DATABASE EMBL SEQ. [Online] Accession No. HS944183, 6 August 1995 (1995-08-06) 'EST; H. sapiens cDNA clone IMAGE:187152' XP002152483

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Since the Applicant wished to have only invention 1 examined, claims concerning invention 2 (claims 18, 19 (entirely); claims 1, 6, 8-16 (partially)) are not examined here.

**Re Item IV**

**Lack of unity of invention**

The IEA agrees with the objection for lack of unity raised by the ISA. The present application was found to concern the following two groups of inventions:

Invention 1 (2-5, 7, 17 (entirely); 1, 6, 8-16 (partially))

A DNA construct comprising a transcriptional regulatory sequence operatively linked to a heterologous gene of interest, wherein the transcriptional regulatory sequence comprises the eIF4A gene promoter, a fragment thereof or a polynucleotide hybridisable thereto, and further comprises at least the eIF4A intron, fragment thereof or polynucleotide hybridisable

**INTERNATIONAL PRELIMINARY  
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thereto.

Recombinant host cells, methods of production, pharmaceutical compositions, therapeutic applications.

An isolated polynucleotide having a sequence as set forth in SEQ. IDs 31-37, a fragment thereof or a polynucleotide hybridisable thereto.

Invention 2 (claims 18, 19 (entirely); claims 1, 6, 8-16 (partially))

A DNA construct comprising a transcriptional regulatory sequence operatively linked to a heterologous gene of interest, wherein the transcriptional regulatory sequence is an eIF4A gene promoter fragment selected from -526EIF, -371EIF, -271EIF, -193EIF, -120EIF, -98EIF, -69IEF, -40IEF, and seq. ID 38.

Recombinant host cells, methods of production, pharmaceutical compositions, therapeutic applications.

An isolated polynucleotide having a sequence as set forth in seq. ID 40 at position -2102 and -1082 or at positions -1107 to -505, or respective fragments thereof or polynucleotides hybridisable thereto.

Prior art discloses constructs based on the promoter region of the human eIF4A (Kukimoto, BBRC 233:844-847, 1997)

In the light of the prior art, the problem addressed in the present application can be defined as the provision of further such constructs. The solutions proposed are constructs comprising a portion of the eIF4A promoter region (1) with or (2) without a further regulatory element derived from at least an eIF4A intron sequence.

Whereas, constructs based on the promoter region of the human eIF4A gene are known from prior art, the solutions to the problem are essentially different. No further technical feature can be identified which, in the light of prior art, could have been considered as a special feature common to all of the solutions.

Therefore, the IEA is of the opinion that not all of the inventions claimed in the present application are so linked as to form a single, general inventive concept in the sense of Rule 13 PCT. Consequently, the application lacks unity of invention.

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The Applicant's attention is drawn to the fact that the subject-matter of the group of inventions 2 may be split in as many inventions as different constructs are claimed since sequences comprising the human eIF4A promoter and constructs comprising them are known from prior art.

The Applicant wished to have invention 1 examined. Thus, the present opinion concerns this group of inventions.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Reference is made to the following documents cited in the International Search Report:

D1: KUKIMOTO I. ET AL.: 'Characterization of the cloned promoter of the human initiation factor 4AI gene' BIOCHEM. BIOPHYS. RES. COM., vol. 233, 1997, pages 844-847, XP002152479 cited in the application

D2: WO 97 42337 A (GLAXO GROUP LTD ;GREAVES DAVID ROBERT (GB)) 13 November 1997 (1997-11-13)

D3: DATABASE EMBL SEQ. [Online] Accession No. HS944183, 6 August 1995 (1995-08-06) 'EST; H. sapiens cDNA clone IMAGE:187152' XP002152483

D4: DATABASE EMBL SEQUENCES [Online] Accession No. HS011206, 7 October 1995 (1995-10-07) 'EST; H. sapiens cDNA clone IMAGE:204614 similar ro eukaryotic initiation factor 4A-I.' XP002152484

D5: DATABASE EMBL SEQUENCES [Online] Accession No. HSU79273, 14 December 1996 (1996-12-14) ANDERSSON B.: 'Human clone 23933 mRNA' XP002152485

D6: DATABASE EMBL SEQUENCES [Online] Accession No. AB011595, 10 March 1998 (1998-03-10) 'Mouse eIF4A gene' XP002152486 -& MIYASHITA A. ET AL.: 'Five different genes, Eif4a1, Cd68, Supl15h, Sox15 and Fxr2h, are clustered in a 40 kb region of mouse chromosome 11' GENE, vol. 237, no. 1, 3 September 1999 (1999-09-03), pages 53-60, XP004183497

1. Novelty (Art. 33(2) PCT)
  - 1.1 The applicant's attention is drawn to the fact that a "fragment" of a polynucleotide can be a single nucleotide. Consequently, claim 17 is directed to an isolated polynucleotide having a sequence as set forth in SEQ ID No: 31-37, or a fragment thereof (at least one nucleotide). Therefore, any polynucleotide having at least one

nucleotide in common with any of these sequences is novelty destroying to claim 17.

Concerning this, it is noteworthy that a polynucleotide can always be considered to be able to hybridize to another polynucleotide depending on the experimental conditions, the sequence distribution, etc. Thus, in the absence of specification that the hybridizable polynucleotide has the same function as the sequences claimed in claim 17 and without the specification of a percentage of identity over the entire sequence (which should be defined), the unclarity of said claim also leads to an objection for lack of novelty. Concerning this, the Applicant's attention is drawn to the fact that both human and mouse eIF4A promoters were characterized and shown to have 80% homology between them (see D1 and D6).

Consequently, claim 17 is not novel, and thus, not inventive.

2. Inventive step (Art. 33(3) PCT)

Prior art discloses constructs based on the promoter region of the human eIF4A (D1, Kukimoto, BBRC 233:844-847, 1997)

In the light of the prior art, the problem addressed in the present application can be defined as the provision of further such constructs. The solution proposed are constructs comprising a portion of the eIF4A promoter region in combination with at least one eIF4A intron.

Inventive activity could be acknowledged for the specific combinations between the eIF4A promoter (defined by its sequence) and the eIF4A introns (defined by their sequence) since there seems to be no suggestion from the prior art to combine the eIF4A promoter with at least one of its introns to achieve higher expression, and increased permanence of expression, when compared with viral promoter systems.

DNA molecules comprising either the eIF4A promoter or at least an eIF4A intron independently cannot be acknowledged inventive activity since such molecules existed already (claims 1, 11 (partially), 17). Concerning this, the Applicant's attention is further drawn to the fact that the genomic sequence 5' of the human CD68 gene is disclosed in D2. It was known that eIF4A is immediately upstream of CD68, and indeed, this sequence comprises portions identical to some of the introns claimed by the present application (97,6% identity between SEQ ID NO 31 and D3; 98, 3%

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02569

identity between SEQ ID NO 32 and D4; 99,7% identity between SEQ ID NO 33 and D5; 100% identity between SEQ ID NO 34, 35, 36, 37 and the 5' region of CD68 (D2). Thus, claims 1, 8 (partially), 9 (partially), and 17 are not inventive because of this reason.

**3. Industrial applicability (Art. 33(4) PCT)**

For the assessment of the present claims 12 and 15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VII**

**Certain defects in the international application**

Concerning the expression "spirit and scope of the invention" found at page 14, the Applicant's attention is drawn to the Guidelines III-4.3a PCT.

**Re Item VIII**

**Certain observations on the international application**

**1. Clarity (Art. 6 PCT)**

1.1 The Applicant's attention is drawn to the fact that claim 9 may be directed to a cell in a host which can be a human being; and therefore may be considered by the present IPEA to be contrary to morality, and hence, not allowable.

**2. Support by specification (Art. 6 PCT), in combination with Art. 5 PCT (complete and enabling disclosure)**

The present set of claims covers human/mouse combinations which have no basis in the application as filed.

**PATENT COOPERATION TREATY**

From the INTERNATIONAL SEARCHING AUTHORITY

**PCT**

To:  
**GLAXO WELLCOME PLC**  
 Glaxo Wellcome House  
 Attn. REES, Marion  
 Berkeley Avenue  
 Greenford  
 Middlesex UB6 0NN  
 UNITED KINGDOM

NOTIFICATION OF TRANSMITTAL OF  
 THE INTERNATIONAL SEARCH REPORT  
 - 2 FEB 2001 OR THE DECLARATION

(PCT Rule 44.1)

TLP HLR

Date of mailing (day/month/year)	02/01/2001
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Applicant's or agent's file reference

PG3717 ~~HLR PCT~~

**FOR FURTHER ACTION** See paragraphs 1 and 4 below

International application No.

PCT/GB 00/02569

International filing date

(day/month/year) 05/07/2000

Applicant

GLAXO GROUP LIMITED et al.

1.  The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland  
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2.  The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3.  With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau.

If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  
  
 European Patent Office, P.B. 5818 Patentlaan 2  
 NL-2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Carla Louro



## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

**The amendments must be made in the language in which the international application is to be published.**

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

**The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.**

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

**The following examples illustrate the manner in which amendments must be explained in the accompanying letter:**

1. [Where originally there were 48 claims and after amendment of some claims there are 51]: "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]: "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PATENT COOPERATION TREATY

PCT

**NOTIFICATION OF ELECTION**  
 (PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
**ETATS-UNIS D'AMERIQUE**

in its capacity as elected Office

Date of mailing (day/month/year) 14 March 2001 (14.03.01)	To:  Commissioner US Department of Commerce United States Patent and Trademark Office, PCT 2011 South Clark Place Room CP2/5C24 Arlington, VA 22202 <b>ETATS-UNIS D'AMERIQUE</b> in its capacity as elected Office
International application No. PCT/GB00/02569	Applicant's or agent's file reference PG3717
International filing date (day/month/year) 05 July 2000 (05.07.00)	Priority date (day/month/year) 06 July 1999 (06.07.99)
<b>Applicant</b>  GREAVES, David, Robert et al	

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

26 January 2001 (26.01.01)

in a notice effecting later election filed with the International Bureau on:

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  Juan Cruz  Telephone No.: (41-22) 338.83.38
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## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

REES, Marion  
 GlaxoSmithKline  
 Corporate Intellectual Property  
 Two New Horizons Court  
 Brentford  
 Middlesex TW8 9EP  
 ROYAUME-UNI

Date of mailing (day/month/year) 06 juillet 2001 (06.07.01)	
Applicant's or agent's file reference PG3717	<b>IMPORTANT NOTIFICATION</b>
International application No. PCT/GB00/02569	International filing date (day/month/year) 05 juillet 2000 (05.07.00)

## 1. The following indications appeared on record concerning:

the applicant     the inventor     the agent     the common representative

Name and Address  REES, Marion Glaxo Wellcome PLC Berkeley Avenue Greenford, Middlesex UB6 0NN United Kingdom	State of Nationality	State of Residence
	Telephone No.	020 8966 5728
	Facsimile No.	020 8966 8838
	Teleprinter No.	

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person     the name     the address     the nationality     the residence

Name and Address  REES, Marion GlaxoSmithKline Corporate Intellectual Property Two New Horizons Court Brentford Middlesex TW8 9EP United Kingdom	State of Nationality	State of Residence
	Telephone No.	020 8966 8412
	Facsimile No.	020 8966 8838
	Teleprinter No.	

## 3. Further observations, if necessary:

4. A copy of this notification has been sent to:
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the receiving Office     the designated Offices concerned  
 the International Searching Authority     the elected Offices concerned  
 the International Preliminary Examining Authority     other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland  Facsimile No.: (41-22) 740.14.35	Authorized officer  I. Britel  Telephone No.: (41-22) 338.83.38
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